

Section II (Remarks)

A. Summary of Amendment to the Claims

By the present Amendment, claims 1, 18, 19 and 26 have been amended. No new matter within the meaning of 35 U.S.C. §132 has been introduced by the foregoing amendments. Specifically, support for the amendments to claims 1 and 18 can be found in the specification at page 5, paragraph [0015], in the description of the embodiment illustrated in Fig. 1A. Support for the amendments to claims 19 and 26 can be found at page 10, paragraphs [0036]-[0037] and pages 16-17, paragraph [0057].

In view of the finality of the February 25, 2010 Office Action and to ensure substantive consideration of this response, a Request for Continued Examination is concurrently submitted herewith, together with payment of the appertaining RCE fees (see *infra*, "CONCLUSION").

B. Rejection of claims 1, 6-9 and 23-26 under 35 U.S.C. §102

In the Office Action mailed February 25, 2010 the examiner maintained the rejection of claims 1, 6-19 and 23-26 under 35 U.S.C. §102(b) as anticipated by U.S. Patent No. 6,214,205 (hereinafter "Willner et al."). Applicants respectfully disagree.

The examiner alleged that Willner et al. teaches each step of the method of independent claim 1, the method of independent claim 18 and the biosensor of independent claim 26. Claims 6-17, 19 and 23-25 depend directly or indirectly from independent claims 1 or 18 and, by virtue of their dependency, contain all elements of claims 1 or 18.

In the Response mailed December 2, 2009, applicants noted that both of claims 1 and 18 recite a method where the capture molecule is immobilized at the surface of the electrode and forms a complex with the analyte and where the complex is a first layer on the electrode (step (c)). Subsequently, the electrode is contacted with an electrochemical activator, forming a second layer on the electrode (step (d)). Together these components form a conducting bilayer on the electrode.

In order to clarify the sequential aspect of the method, claims 1 and 18 have been amended as set forth in Section I above. As amended, the claims include recitation of the order of the steps of

the claimed method. The claimed method proceeds sequentially from step (a) to step (g) in claim 1 and sequentially from step (a) to step (e) in claim 18.

By recitation of the stepwise aspect of the method, it is clear that the electrochemical activator is contacted with the detection electrode (step (d)) after the complex between the analyte and the capture molecule has been formed (step (c)). The electrochemical activator “has an electrostatic net charge that is complementary to the electrostatic net charge of the complex formed between a capture molecule and an analyte molecule.” However, it is the presence of the analyte that results in a measurable electric current.

By contrast, in Figures 13A-13C of Willner et al., the presence of an analyte has the effect that no electrical current can be measured (*see* voltamograms of Fig. 13A-C). The detection of the analyte is made by interruption of the current between glucose oxidase (GOD) and the electrode.

In the Office Action mailed February 25, 2010 the examiner “does recognize the difference between the disclosure of [the] application and the prior art reference...” (Final Office Action, p. 10). However, the examiner maintained that:

“Instant claim 1 claims a method of detecting the analyte based on formation of first and second layer. Willner teaches the formation of a first layer *i.e.* immobilizing the electrode with capture molecule and analyte to form complexes and second layer *i.e.* contacting the electrode with first redox molecule...Willner further teaches the current can be detected when both the first and second layers are present in the electrode...”

In support of the latter statement, the examiner again cited Figures 13A-13C. In the analysis of claim 1 at pages 3-4 of the Final Office Action, the examiner referred specifically to both Figures 3A-3B and 13A-13C as anticipatory of claim 1.

In discussion of step (d) of the applicants’ claimed invention, the examiner contended that Figs. 3A-C and 13A-C were anticipatory of the “contacting” of applicants’ step, where step (d) of applicants’ claimed invention is as follows:

(d) contacting the detection electrode with an electrochemical activator, wherein said electrochemical activator has a electrostatic net charge that is complementary to the electrostatic net charge of the complex formed between a capture molecule and an analyte molecule, thereby forming a second layer on the electrode, wherein the second layer and the first layer together form a conducting bilayer; subsequently

This contention is not correct. The embodiments illustrated in Figures 3 and 13 differ from one another and neither is anticipatory of applicants' claimed invention.

In the discussion of the anticipation of step (d) of claim 1 of applicants' claimed invention by Fig. 3C, the examiner identified the first redox molecule as equivalent to applicants' recited "electrochemical activator." However, by examination of Fig. 3C of Willner et al. it can be seen that the first redox molecule 26 is already bound to the electrode and is not separately contacted with the detection electrode, as is required by applicants' claim 1, step (c). Therefore Fig. 3 is not anticipatory of step (d) of claim 1.

Generally, Figure 13 of Willner et al. provides an electrode with ferrocene acting as the first redox molecule, glucose oxidase (GOD) as the second redox molecule, and glucose as the substrate. As compared to applicants' claim terminology, it appears that the examiner equates the Δ to applicants' "capture molecule," the Ab to applicants' "analyte" and the GOD to applicants' "electrochemical activator." Accordingly, with respect to step (c) of claim 1, the examiner characterized applicants' claimed complex between a capture molecule and an analyte molecule forming a first layer on the detection electrode as being comparable to the Δ -Ab interaction, as illustrated in the boxed portion of Figure 13C of Willner et al, below:

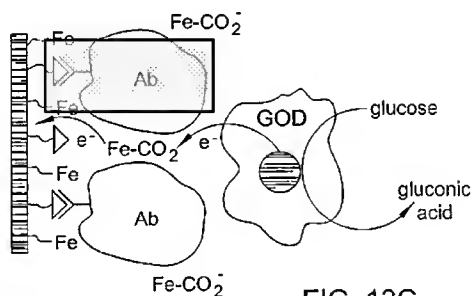


FIG. 13C

In response, the examiner's attention is respectfully drawn to the following language of step (d) of applicants' claimed invention: "wherein said electrochemical activator has an electrostatic net charge that is complementary to the electrostatic net charge of the complex formed between a capture molecule and an analyte molecule."

An enzyme, such as GOD, cannot be said to have the same electrostatic net charge as the analyte to be detected since the net charge of an enzyme, such as GOD, is fixed due to the natural composition of the enzyme and not variable, *i.e.* it is not adaptable to the charge of the complex formed between the capture molecule and the analyte molecule.

Furthermore, the GOD is present from the beginning of the detection method illustrated in Fig. 13 (see Fig. 13A), even before Ab addition, unlike applicants' claimed method in which the forming of a layer on a detection electrode, comprising the capture molecule and analyte molecule complexes, is subsequently followed by contacting with an electrochemical activator.

With regard to the examiner's assertion that "Willner further teaches the current can be detected when both the first and second layers are present in the electrode....," applicants again direct the examiner's attention to Figs. 13A-C. As described at col. 6-7, the figures illustrate the function of an electrode 1) prior to exposure to antibodies (Fig. 13A), 2) after exposure to antibodies and formation of complexes (Fig. 13B), and 3) upon addition of Fe-CO₂ (Fig. 13C). Contrary to the examiner's assertion, where the Δ-Ab complexes are formed and the GOD is present, no electrical current is flowing (Fig. 13B; "[n]o electrocatalytic oxidation of glucose"). This can be seen in the boxed portion of Fig. 13B:

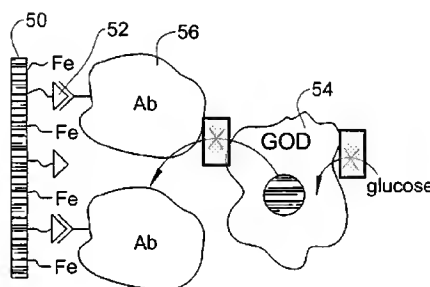


FIG. 13B

Only upon addition of Fe-CO₂ (Fig. 13C) does the electrocatalytic oxidation resume.

Therefore the methods of detection of an analyte as described in Willner et al. differ fundamentally from applicants' claimed methods, in that in Willner et al. the analyte is detected by the interruption of current and in applicants' claimed method the analyte is detected by the presence of current.

The electrode arrangement of claim 19 and the biosensor of claim 26 are arranged to optimize this detection of an analyte by detection of current. In order to emphasize this aspect of the invention, the claims have been amended to recite "wherein detection of the analyte molecule is indicated by the flow of an electrical current..." Willner et al. does not provide such an electrode arrangement or biosensor.

Willner et al. fails to provide a method for the electrochemical detection of an analyte molecule, where the method comprises a stepwise attachment of a first layer, then a second layer to an electrode to form a detection electrode, wherein the electrochemical activator is contacted with the detection electrode after the complex between the analyte molecule and the capture molecule has been formed and wherein the analyte is detected by the presence of an electrical current. Willner et al. also fails to provide a resulting electrode arrangement or biosensor in which the electrochemical activator has an electrostatic net charge that is complementary to the electrostatic net charge of the complex between the analyte molecule and the capture molecule and in which the presence of the analyte is detected by the flow of an electrical current.

Since Willner et al. do not describe a method as set forth in claim 1 or claim 18, or an electrode arrangement as set forth in claim 19, or a biosensor as set forth in claim 26, Willner et al. do not anticipate the claimed invention. Claims 6-17, 19 and 23-25 depend directly or indirectly from claim 1 and therefore are patentable for the same reasons advanced above in support of the patentability of claims 1 and 18.

Accordingly, withdrawal of the rejection of claims 1, 6-19 and 23-26 under 35 U.S.C. § 102(b), as being anticipated by Willner et al., is respectfully requested.

C. Rejection of the claims under 35 U.S.C. §103

In the February 25, 2010 Final Office Action, claims 2-4 and 20-22 were rejected under 35 U.S.C. §103(a) as being unpatentable over Willner et al. (U.S. Patent No. 6,214,205) as applied to claims 1, 6-18 and 23-25 and further in view of Zhiqiang et al. (Electrodeposition of Redox Polymer and Co-Electrodeposition of Enzymes by Coordinative Crosslinking, *Angew. Chem. Int. Ed.*, 2002, 41, 810-813).

Additionally, claim 5 was rejected under 35 U.S.C. §103(a) as being unpatentable over Willner et al. as applied to claims 1, 6-18 and 22-25 and further in view of Zhiqiang et al. and U.S. Patent No. 6,299,757 (hereinafter "Feldman et al.").

Each of the rejections set forth under 35 U.S.C. §103(a) relies on Willner et al. as a primary reference. As set forth in detail above, Willner et al. do not anticipate any of claims 1, 6-19 or 23-26. Rejected claims 2-5 and 9-21 depend, directly or indirectly from claim 1 or 18 and are therefore patentable for the same reasons advanced above in support of the patentability of claim

1. Neither of cited secondary references Zhiqiang et al. nor Feldman et al. remedies the deficiencies of Willner et al.

As set forth in detail above, the measuring principle of analyte detection taught by Willner et al. differs from the measuring principle in the method of applicants' claimed invention. In brief, the presence of an analyte in Willner's method has the effect that no electrical current can be measured (*see* Figure 13B of Willner et al.) whereas in applicants' claimed methods, only the presence of the analyte results in a measurable electrical current (*see* Figure 1A).

Though Fig. 13C of Willner et al. illustrates an embodiment of that method in which a solubilized ferrocene monocarboxylic acid (Fe-CO₂) is added, the addition of Fe-CO₂ does not result in the detection of the analyte (*see* Willner et al, col.15, line 57 to col.16, line 10). As illustrated by the cyclic voltammogram in each of Figures 13A to 13C, the detection of the analyte is indicated by an interruption of the current between GOD and electrode (compare cyclic voltammograms of Figure 13A and 13B). The addition of Fe-CO₂ merely serves to verify that the current flow is indeed hindered by the steric blockage caused by the bulky analyte (56) but it does not serve as a step necessary to prove that the analyte is present. In fact, the claims of Willner et al. do not recite that addition of a molecule, such as Fe-CO₂ is necessary to demonstrate that the analyte is present. Thus, the measuring principle is fundamentally different between the subject matter of present claim 1 and the method taught by Willner et al.

Furthermore, Willner et al. does also not provide any derivative basis for the measuring principle utilized in the method of the present invention. Additionally, there would have been no logical reason for one of skill in the art to attempt to modify the measuring principle of Willner et al. by combining Willner et al. with additional references to achieve applicants' claimed invention.

Zhiqiang et al. is cited by the examiner as "teach[ing] a polymeric redox polymer deposit on the electrodes which further conducts electron transfer to oxidized/reduced substrates of the enzyme...[that t]he redox polymers are water soluble and readily bound to proteins and enzymes...[and] that polymeric redox polymer comprises osmium metal ions coordinated with the ligands." Based on the foregoing, Willner et al. in view of Zhiqiang et al. fail to provide any logical basis for a method comprising use of an electrode with an analyte-containing bilayer that is capable of electron flow formed thereon.

The combination of Willner et al. and Zhiqiang et al. fails to render the method of claims 2-4 and 20-22 obvious. Accordingly, withdrawal of the rejection of claims 2-4 and 20-22 under 35 U.S.C. § 103(a) as being obvious over Willner et al. in view of Zhiqiang et al. is respectfully requested.

The further citation of Feldman et al. fails to provide any logical basis in the combination of Willner et al. and Zhiqiang et al. for a method comprising use of an electrode with an analyte-containing bilayer that is capable of electron flow formed thereon.

Feldman et al. is a newly cited reference since the last Response provided by applicants. Specifically, Feldman et al. is cited as “teach[ing] a redox mediator comprised of poly(vinyl ferrocene) to increase swelling of the redox polymer in water...”

The combination of Willner et al., Zhiqiang et al. and Feldman et al. fails to render the method of claim 5 obvious. Accordingly, withdrawal of the rejection of claim 5 under 35 U.S.C. § 103(a) as being obvious over Willner et al. , Zhiqiang et al. and Feldman et al. is respectfully requested.

CONCLUSION

Based on the foregoing, all of applicants’ pending claims 1-26 are patentably distinguished over the art, and in form and condition for allowance. The examiner is requested to favorably consider the foregoing, and to responsively issue a Notice of Allowance.

The time for responding to the February 25, 2010 Office Action without extension was set at three months, or May 25, 2010. Applicants hereby request a one month extension of time under 37 CFR § 1.136 to extend the deadline for response to July 25, 2010. Payment of the extension fee of \$490.00 specified in 37 C.F.R. § 1.17(a)(2) and the RCE fee of \$810.00 specified in 37 C.F.R. § 1.17(e), as applicable to large entity, is being made by on-line credit card authorization at the time of EFS submission of this Response. Should any additional fees be required or an overpayment of fees made, please debit or credit our Deposit Account No. 08-3284, as necessary.

If any issues require further resolution, the examiner is requested to contact the undersigned attorneys at (919) 419-9350 to discuss same.

Respectfully submitted,

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